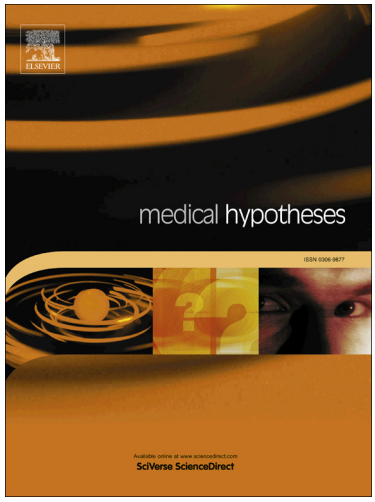

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Rachel Gimenes Albuquerque, Keity Mey Okazaki, Camila Hirotsu, Jane Tomimori, Sergio Tufik, Monica Levy Andersen

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Sleep, Hansen's disease and the immune system – a not so harmonic triad

Rachel Gimenes Albuquerque*[1]; Keity Mey Okazaki*[1]; Camila Hirotsu[1], PhD; Jane Tomimori[2], MD, PhD; Sergio Tufik[1], MD, PhD; Monica Levy Andersen[1], PhD

*Both authors equally contributed to the manuscript

Universidade Federal de São Paulo

[1]Department of Psychobiology – Rua Napoleão de Barros, 1038 - Vila Clementino - 04024-003 - São Paulo, SP, Brazil

[2]Department of Dermatology - Rua Borges Lagoa, 508 - Vila Clementino - 04038-001, São Paulo, SP, Brazil

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Corresponding author:

Camila Hirotsu, PhD

Phone: (55) (11) 5908-7193

Fax: (55) (11) 5572-5092

Address: Rua Marselhesa, 529 - Zip code: 04020-060, Sao Paulo (SP), Brazil

E-mail: milahirotsu@gmail.com

Abstract

Hansen's disease is one of the oldest skin diseases in the world characterized by a spectrum of clinical manifestations that are associated with stigmatization and poor quality of life. It is also considered a model disease for investigating the human immune system because of its association with immune reactions, which are thought to be a reflection of the host's immunological response, promoting intense cellular activity or humoral secretion. This relationship between the cellular and microbial components of skin and their regulation by local immune responses may be modulated by a currently neglected behavior: sleep. Recent studies have demonstrated that sleep deprivation may aggravate the progression of chronic dermatological diseases, which in turn can lead to a non-restorative sleep pattern. Indeed, sleep is essential for immune and skin integrity. Thus, we propose here a hypothesis linking Hansen's disease, sleep and immunity in a bidirectional relationship. Hansen's disease patients may demonstrate a worse sleep quality than the general population through the modulation of immunological environment; and sleep restriction, a hallmark of modern society, being a possible predictor of the disease progression.

Key-words: Hansen's disease; sleep; immune system; sleep disorders.

Introduction

Skin diseases have been present in humanity for thousands of years and in some religions have been considered a punishment for sin. The sacred scriptures mention the hebrew word zara'at, which was used generically to describe pathological conditions of hair and skin (1). Hansen's disease or hanseniasis, which is more commonly known as leprosy, is tied to human history (2), frequently accompanied by social and religious stigma, and also segregation (3, 4). The discovery of the etiological agent, *Mycobacterium leprae,* in the XIX century brought increased knowledge about the transmission, pathogenesis, treatment and prevention of the disease (5). However, the World Health Organization (WHO) still seeks to eradicate this disease. About 232,857 new cases of leprosy were registered during 2012 in 115 countries. From these cases, 95% were from 16 developing countries, and only 5% were from the remaining countries in the world, suggesting that Hansen's disease is still a very significant malady in certain regions (6). The prevalence in endemic areas has been decreasing in the last 10 years, although the incidence has remained about the same (7).

Based on clinical, histological and immunological differences, clinical manifestations of Hansen's disease are classified in 5 types: tuberculoid (TT), mid-borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL) and lepromatous (LL). At one end pole of the spectrum, TT shows few lesions, which are well-defined, and bacteria are rarely detected. TT skin lesions primarily consist of epithelioid macrophages surrounded by $CD4^+$ T lymphocytes that help other cells of the immune system (8). At the other pole, LL presents multiple, symmetrically distributed lesions throughout the body,

including nerves, eyes and internal organs, besides skin. Lesions are characterized by foamy macrophages infiltrate and a few lymphocytes, predominantly $CD8^+$ T cells, also known as cytotoxic T cells due to their capacity to kill infected or damaged cells by cytotoxicity (8).

As Hansen's disease presents a close connection to the immunological context, sleep has been extensively described to modulate the integrity of the immune system (9-12). Bearing this in mind, we present a discussion about a possible bidirectional relationship between sleep and Hansen's disease, focusing on disease progression, sleep disorders and the immune system.

Hansen's disease

First, it is important to highlight some characteristics of the pathogenic agent of Hansen's disease. The *Mycobacterium leprae* is a highly infective bacterium with low pathogenicity and virulence. The progression of the disease is slow due to the long incubation period of the bacteria. Also, since it prefers temperatures lower than 37ºC, it usually infects the skin, testis and peripheral nerves (7). Most people infected by the bacteria do not develop the disease. The first signs of the clinical disease are mild; patients normally present hypoesthesia and hypopigmented macule on the skin. The progression of the disease depends on the immune responses of the host.

In general, the treatment indicated for Hansen's disease by the WHO is a multidrug therapy, composed of rifampicin, clofazimine and dapsone (13). A significant percentage of the patients may develop reactions mainly during or after the disease treatment (14). The leprosy reactions are known as type 1 and type 2 and are examples of cell mediated hypersensitivity reactions and

humoral hypersensitivity reactions, respectively. Type 1 reaction, also known as reversal reaction, tends to occur in cases of the borderlines BT, BB and BL; it is described as an aggravation of the lesions. Type 2, or erythema nodosum leprosum (ENL) reaction, is more frequent among LL patients and occasionally in BL. It is more aggressive, involving fever, worsening of lesions, and pain (7).

Immunological parameters of Hansen's disease

A different immune response is observed in each of the 5 categories, especially when comparing the 2 poles, TT and LL. In general, TT demonstrates a high cell-mediated immunity and a largely Th1 type immune response. However, LL presents a low cell-mediated immunity and a Th2 type response (15). Immunohistology of skin lesions shows that while there are more $CD4^+$ than $CD8^+$ T lymphocytes in the TT type, the opposite occurs in the LL type, where $CD8^+$ T cells predominate (16). Cytokines' patterns also differ when comparing the 2 forms of the disease, and their discovery played an important part in helping identify the predominance of Th1 response in TT and Th2 in LL type. Through polymerase chain reaction (PCR), it was demonstrated that TT lesions have higher levels of IL-2 and IFNγ mRNA, whereas IL-4, IL-10 and IL-5 were prominent in LL lesions (15). Serum analysis demonstrated that patients with Hansen's disease, in general, present increased levels of IFNγ, IL-10, IL-1β and TNFα in comparison to normal patients. Still comparing the 2 poles of the disease, TT patients showed higher levels of TNFα and IFN-gamma, while LL patients had increased levels of IL-10 and IL-1beta (17). In fact, Hansen's disease is not only a skin malady, but also a severe immunological disease. The 2 poles exhibit distinct immunological patterns, reinforcing this tight

connection between the skin and the immune system. Besides skin, sleep also plays a fundamental role in the regulation of the immune system. Thus, sleep quality may be another important factor that may affect the progression of Hansen's disease.

Sleep and the immune system

A bidirectional relationship between sleep and the immune system has been demonstrated by some studies (18), revealing that immune functions are synchronized with the 24-hours sleep-wake cycle, including cytokine secretion, lymphocyte circulation and the defense cells' activity (18). The central nervous system is able to detect peripheral immunological activation through the stimulation of nerve fibers through circulating cytokines that permeate the organs and the blood–brain barrier, and through brain-derived cytokines (19). Also, cytokines are synthesized and released in the central nervous system by both neurons and glia, and neurons immunoreactive to IL-1 and TNFα are located in brain regions involved in sleep-wake cycle regulation such as the hypothalamus and brainstem. Particularly, proinflammatory cytokines promote non-REM (NREM) sleep, whereas anti-inflammatory cytokines inhibit NREM sleep (20).

In addition, knockout mice for IL-1β and TNF-α receptors showed an increase in non-rapid eye movement (NREM) sleep, confirming an important function of cytokines in sleep regulation (21). Palmblad and collegues (22, 23) were the first to describe the effects of total sleep deprivation (TSD) in humans. In different protocols, they found that TSD increased IFNγ production by lymphocytes and decreased lymphocyte blastogenesis. Several studies were

conducted thereafter which demonstrated that TSD also impairs NK cell activity, increases leukocyte count for IL-1β and IL-1 receptor antagonist (IL-1Ra), and decreases IL-6 count (24, 25). More recently, a study conducted with healthy male volunteers demonstrated that after 2 nights of total sleep deprivation there was an increase in the number of neutrophils and $CD4^+$ T cells, in comparison to baseline (26). In addition, after 3 nights of sleep recovery, the percentage of CD4+ T cells did not return to the basal levels. Volunteers who underwent selective REM sleep deprivation only demonstrated a reduction of IgA levels during the protocol (26). It is possible to assert that partial sleep deprivation (PSD) is also harmful. Irwin and colleagues (27, 28) observed that a partial night of sleep deprivation decreased NK cells' activity as well as IL-2 production. After 1 night of sleep recovery, IL-2 levels remained suppressed.

Sleep and skin diseases

Recently, some studies were conducted to evaluate the relationship between sleep and skin diseases. A study conducted by Yang and colleagues (29) showed that patients with obstructive sleep apnea (OSA) have an increased risk to develop psoriasis. Also, it was demonstrated that patients with psoriasis are more likely to develop sleep disturbances than controls (30). Pain, pruritus and depression are also important factors that affect sleep quality in psoriatic patients (31). In cases of atopic dermatitis (AD), especially in children, a poorer sleep quality has been observed in patients. Through polysomnography (PSG) and actigraphy assessment, pediatric patients with AD demonstrated reduced sleep efficiency, sleep fragmentation, longer sleep onset latency and less NREM sleep (11).

In adults, all scratching episodes were associated with arousal or awakening during sleep. The sleep efficiency reported by PSG and actigraphy was significantly correlated with the scratching index (32), confirming the primary impact of AD on sleep quality and secondarily, on quality of life. Regarding Hansen's disease, some studies have concluded that sleep can be possibly impaired due to the neuropathic pain that leprosy promotes (33-35). Also, psychiatric disorders are commonly seen in patients with this disease. A study conducted by Rocha-Leite and colleagues (36) showed that in a sample of 120 Hansen's disease patients, 37 (30.8%) were diagnosed with depression, 18 (15%) had obsessive compulsive disorder and 11 (9.2%) were diagnosed with generalized anxiety disorder. Importantly, psychiatric disorders have a bidirectional relationship with sleep. Sleep disorders, such as insomnia, can predispose patients to psychiatric disorders, can be comorbid with and exacerbate psychiatric disorders, and can occur as part of psychiatric disorders (37). Also, sleep disturbances may mimic psychiatric disorders or result from treatment for psychiatric disorders. However, until now no study objectively evaluated sleep in Hansen's disease patients. Choi and colleagues (38) used a well-known questionnaire, the Pittsburgh Sleep Quality index, to assess sleep quality. Compared with controls, Hansen's disease patients demonstrated a higher prevalence of restless leg syndrome. Importantly, those who presented RLS reported a worse quality of sleep.

The hypothesis

As previously described, Hansen's disease patients may develop immune reactions during treatment, ranging from immune cellular to humoral

response. As sleep is strongly influenced by immunity, being altered in several immunological diseases and sleep deprivation possibly leading to immunosuppression and inflammation, we hypothesized that Hansen 's disease patients presenting leprosy immune reactions type 1 and type 2 may present some impairment of sleep quality directly linked to their specific immune responses, contributing to the development of sleep disorders, such as insomnia, independent of confounding factors, when compared to Hansen's disease patients without reaction. Also, it is expected that this poor sleep quality mediated by immune reaction in addition to the sleep deprivation, a common event on the modern society, will change immunological parameters, increasing inflammation and thus, aggravating the disease manifestation in a vicious cycle.

Consequences of the hypothesis and discussion

Hansen's disease is a well-known disease that worsens the quality of life of many individuals through the stigmatization they feel and the physical and psychological alterations that the progression of disease can inflict. One aspect of the disease that has not been thoroughly explored is its possible relationship with sleep. Hansen's disease has been known to be closely associated with immunity, with different immune responses resulting in distinct types of the disease, and possibly, different effects on sleep pattern. The immune system also has a bidirectional relationship with sleep. Thus, it is very plausible to assert that Hansen's disease patients have a worse quality of sleep compared to the general population, due to the influence of immune response on the central nervous system, possibly in areas also related to sleep-wake regulation. Moreover, poor sleep quality may not only be a consequence of the disease,

but also a consequence of the stigma suffered by patients and that may importantly affect mood and behavior, increasing the anxiety or depression symptoms, and thus also affecting sleep (Figure 1). Lastly, there is growing pressure on time for sleep in the modern world, especially in third world countries, where Hansen's disease prevalence is higher.

Thus, it is important to be aware of the role of sleep on Hansen's disease progression, and its potential role as a predictor of its complications, such as the immune reactions. Sleep can be evaluated by questionnaires, which are easy and very important tools, or even by objective measures as polysomnography and actigraphy. In parallel, immune response can be further investigated through flow cytometry assays. In this way, future researches focused on the intersection of neurophysiology and immunology in Hansen's disease may provide important advances in treatment approaches of the Dermatology field.

Conflicts of interest

The authors declare that, except for income received from primary employer, no financial support or compensation has been received from any individual or corporate entity for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

Figure legend

Figure 1. Schematic representation of the bidirectional relationship between the triad Hansen's disease, sleep and immune system and its interaction with poor quality of life.

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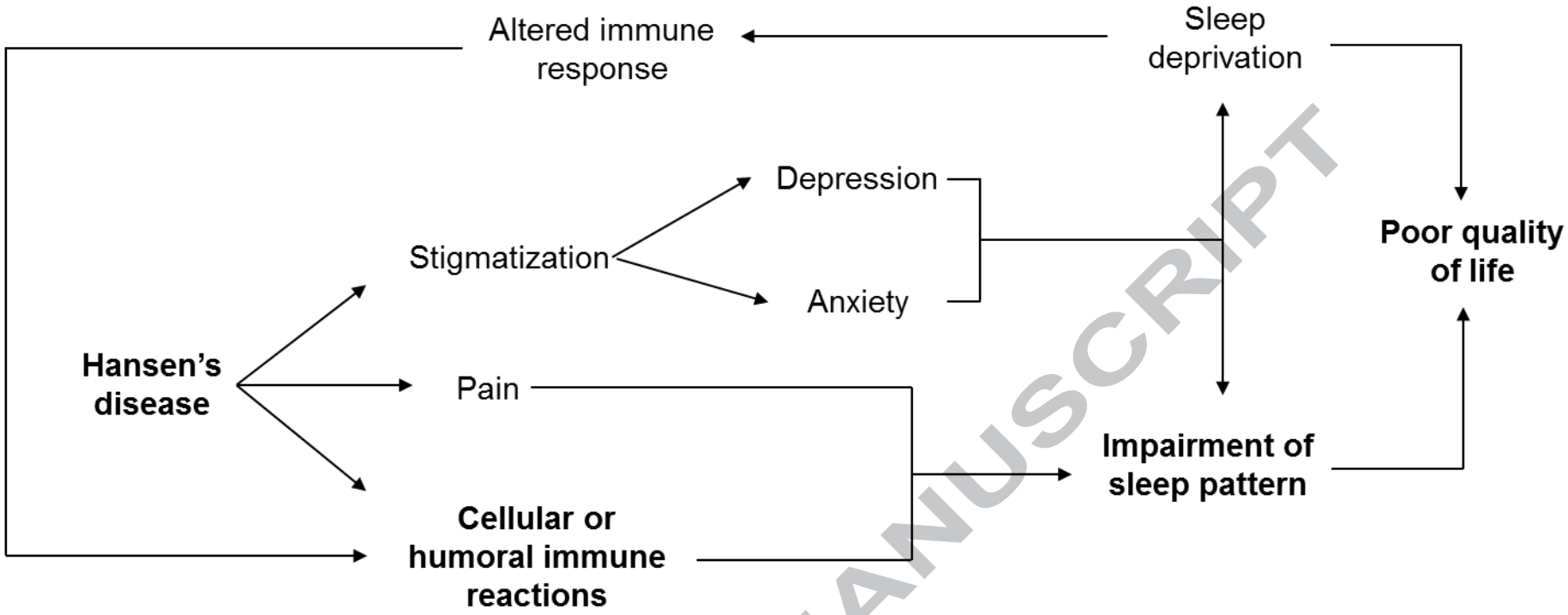

Figure 1. Schematic representation of the bidirectional relationship between the triad Hansen's disease, sleep and immune system and its interaction with poor quality of life.

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